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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/758,970	01/16/2004	Michael Tyo	08191-012002	6224

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EXAMINER	
POPA, ILEANA	
ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
01/05/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/758,970	TYO ET AL.	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/15/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-55 are pending and under examination.

Information Disclosure Statement

2. The IDS form of 10/15/2010 has been considered. It is noted that the Japanese documents 2-49718 and10-51197 have been lined through because the applicant did not provide an English translation of the documents, nor did the applicant provide an English abstract.

Response to Arguments

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1, 2, 12-14, 16-19, 23, 25, 32-40, 43-46, 54 and 55 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (J. Virol., July, 1998, 72: 5757-

5731), in view of both Jones et al. (Infection and Immunity, 1996, 64: 489-494) and Chen et al. (U.S. Patent No. 6,537,813).

Chen et al. teach a continuous process for the preparation of nucleic-acid microparticles, the process comprising: **(a)** providing a mixing chamber and a solvent removal device; **(b)** obtaining a first emulsion by mixing an organic solution comprising biodegradable PLG (i.e., a polymeric material) dissolved in dichloromethane (i.e., an organic solvent) with a first aqueous solution comprising a nucleic acid, wherein mixing takes place in the mixing chamber; **(c)** adding a second aqueous solution comprising polyvinyl alcohol (i.e., a surfactant), wherein the polyvinyl alcohol is an emulsion stabilizer; **(d)** continuously emulsifying the first emulsion and the second aqueous solution to form a second emulsion comprising the nucleic acid, PLG, water and organic solvent; **(e)** transferring the second emulsion to the solvent removal device which comprises a large quantity of water; **(f)** forming an aqueous suspension of nucleic acid-containing microparticles by the diffusion of the organic solvent into the water, wherein diffusion cause the emulsion microdroplets to harden and thus form microparticles (i.e., the solvent removal device is a hardening tank); **(g)** separating the microcapsules from the fluid medium by filtration and removal of the remaining solvent by washing the microcapsules with water; **(h)** drying the microparticles by lyophilization; and **(i)** transferring the dried microparticles into another vessel (claims 1, 12, 13, 16, 18, 23, 25, 35 and 40) (p. 5758, column 1, third full paragraph). Chen et al. do not specifically teach that their mixing chamber is a homogenizer (claim 17), nor do they teach a microparticle size of 0.5 to 2.5 microns (claims 32-34). However, they do teach that the

method is the same as the one taught by Jones et al. (p. 5758, column 1, third full paragraph). Jones et al. teach that the mixing chamber is a homogenizer and that the method results in microparticles with a size of (p. 489, column 2, second full paragraph, p. 490, column 2, first full paragraph). In addition, Jones et al. teach that the PLG has a molecular weight of 50,000 to 70,000 and a ratio of lactide to glycolide is 52:48 (i.e., about 1:1) (claims 37-40) (p. p. 489, column 2, second full paragraph).

Chen et al. and Jones et al. do not teach a scalable continuous process (claim 1), nor do they teach PLGA (claim 36). Chen et al. ('813) teach a scalable, concurrent flow mixing method and apparatus for the preparation of nucleic acid-containing microparticles, wherein the method comprises concurrently introducing and mixing into a flow through mixer (i.e., mixer chamber) at least a nucleic acid-containing solution and a polymer-containing solution to form an uniform microparticle suspension, collecting the suspension in vessels attached to the apparatus, and storing the microparticles in solution or in more concentrated forms, including lyophilized particles; the polymer could be biodegradable PLGA with a molecular weight of 6,000 or 30,000 and a lactic acid/glycolic acid ratio of 50/50 (column 1, lines 15-22; paragraph bridging columns 3 and 4; column 4, lines 12-42; column 13, lines 27-30; paragraph bridging columns 14 and 15; column 19, lines 50-60). Chen et al. teach that their method and apparatus can be adapted for **(i)** the mixing of more than two solution, wherein the mixing of the first components takes place before the introduction of the additional solutions (paragraph bridging columns 9 and 10) and **(ii)** a continuous process (column 21, lines 47-63). It would have been obvious to one of skill in the art, at the time the invention was made, to

modify the method of Chen et al. and Jones et al. by using the apparatus of Chen et al. ('813), with a reasonable expectation of success. The motivation to do so is provided by Chen et al. (813), who teach that no other mixing format allows for convenient, reliable, reproducible, and scalable process that results in the production of uniform quality and particle size specific for different applications (column 6, bridging column 7, column 10 bridging column 11). One of skill in the art would have been expected to have a reasonable expectation of success in doing such because Chen et al. ('813) teach that their apparatus can be successfully adapted for the preparation of microparticles with diverse composition, according to the needs. In addition, it would have been obvious to one of skill in the art, at the time the invention was made, to further substitute the PLG (i.e., poly-lactide-co-glycolide), with PLGA (i.e., poly-lactic-c-glycolic acid) to achieve the predictable result of obtaining nucleic acid-containing microparticles.

With respect to the limitations recited in claims 19, 44-46, 54, and 55, Chen et al. ('813) teach that both the size and uniformity is regulated by controlling the mixing ratio, flow rate, and mixing rate (column 6 bridging column 7). Absent evidence of unexpected results, it would have been obvious to the ordinary skilled artisan to vary the parameters in a given method with the purpose of optimizing the results. Again, absent evidence to the contrary, it is generally not inventive to discover the optimal working conditions of a prior art method, such conditions can be identified by routine experimentation.

With respect to the limitations of the first and second solution having the same osmolarity (claim 2), of the wash solution being sterile water at a temperature of about 2°C to about 8°C (claim 14), of the heating between 30°C and 55°C (claim 21), or of the emulsifying step being carried out between about 2°C to about 8°C (claim 43), absent evidence of unexpected results, it would have been obvious to the one of skill in the art to vary the parameters in a given method with the purpose of optimizing the results. One of skill in the art would have discovered the optimal working conditions by routine experimentation.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

5. Claims 1-6, 12-19, 23, 25, 32-46, 48-50, 54 and 55 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. taken with both Jones et al. and Chen et al. ('813), in further view of both Shah (U.S. Patent No. 6,020,004) and Parikh et al. (U.S. Patent No. 5,660,858).

The teachings of Chen et al., Jones et al. and Chen et al. ('813) are applied as above for claims 1, 2, 12-14, 16-19, 23, 25, 32-40, 43-46, 54 and 55. Chen et al., Jones et al. and Chen et al. ('813) teach lyophilization, they do not specifically teach adding stabilizers such as sucrose and Tris-EDTA before the lyophilization step (claims 3, 4, 15, 41, 42 and 48-50). However, adding such stabilizers to prevent the microparticles from aggregating or fusing during lyophilization was routine in the prior art; the prior art also teaches that these stabilizers could be added to the first aqueous solution (see

Shah, column 6, lines 32-45, column 7, lines 35-38). It would have been obvious to one of skill in the art, at the time the invention was made, to add such excipients before the lyophilization step to achieve the predictable result of stabilizing the microparticles during lyophilization. It is noted that Shah teaches Tris-HCl and not Tris-EDTA. However, it would have been obvious to one of skill in the art to substitute one for the other to achieve the predictable result of stabilizing the microparticles.

Chen et al., Jones et al., Chen et al. ('813) and Shah do not teach a lipid as a stabilizer (claims 5 and 6). Parikh et al. teach using lipids as stabilizers. It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Chen et al., Jones et al., Chen et al. ('813) and Shah by including lipid stabilizers, with a reasonable expectation of success. The motivation to do so is provided by Parikh et al., who teach that the use of lipids results in increased stability during diverse processing steps, such as heating or storage, and also under stress conditions, such as shaking, vibrating, and thermal cycling (column 3, lines 2-6). One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that lipids can be successfully incorporated into microparticles.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

6. Claims 1, 2, 10-14, 16-19, 23, 25-28, 32-40, 43-47, 54 and 55 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. taken with both Jones et

al. and Chen et al. ('813), in further view of both Hartounian et al. (PGPUB 2002/0039596) and Shah.

The teachings of Chen et al., Jones et al. and Chen et al. ('813) are applied as above for claims 1, 2, 12-14, 16-19, 23, 25, 32-40, 43-46, 54 and 55. Although Chen et al., Jones et al. and Chen et al. ('813) teach separating he microcapsules from the fluid medium by filtration through a fine fritted-glass funnel and removal of the remaining solvent by resuspending and washing the microcapsules in water, they do not teach doing such by using a diafiltration apparatus (claims 7-11, 26-28 and 47). Hartounian et al. teach aseptically preparing liposomes by using a diafiltration apparatus such as a hollow fiber filter (p. 2, paragraphs 0020 and 0021, p. 4, paragraph 0062, p. 5, paragraphs 0063-0066, p. 8, paragraphs 0104-0107, p. 9, paragraphs 0112, p. 10, paragraph 0126). It would have been obvious to one of skill in the art, at the time the invention was made, to optimize the production process by employing diafiltration apparatuses, as taught by Hartounian et al. One of ordinary skill in the art would have been motivated to do so in order to enhance the production of large quantities of microparticles for use in the delivery of nucleic acids and to reduce the time in preparing the desired amount of particles. Since the totality of the prior art of record teaches that the microparticles are for *in vivo* use, one of ordinary skill in the art would have been motivated to ensure that all of the components used in the making of the microparticles are sterile, so as to ensure that sterility is preserved throughout the process. One of skill in the art would have been expected to have a reasonable expectation of success in doing so because the art teaches that such methods can be successfully practiced.

With respect to the different residual organic solvent levels recited in claims 10 and 11, Shah teaches that the removal of organic solvent during lyophilization can be monitored (Example 1); therefore, one of skill in the art would only require routine experimentation to achieve and determine these levels.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

7. Claims 1, 2, 12-14, 16-19, 23, 25, 29-40, 43-46, 51-55 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. taken with both Jones et al. and Chen et al. ('813), in further view of Hedley et al. (U.S. Patent 5,783,567).

The teachings of Chen et al., Jones et al. and Chen et al. ('813) are applied as above for claims 1, 2, 12-14, 16-19, 23, 25, 32-40, 43-46, 54 and 55. Chen et al., Jones et al. and Chen et al. ('813) do not specifically teach their nucleic acid as being in the form of circular RNA or supercoiled DNA (claims 29-31 and 51-53). However, one of kill in the art would have expected that either circular RNA or supercoiled DNA molecules are present in the microparticles, because the conditions of encapsulating nucleic acids within microparticles without destroying their structure, thereby allowing for the intracellular delivery of functional RNA or DNA via microparticles, were routine at the time the invention was made, (see Hedley et al., Abstract, column 1, lines 30-58). Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

8. Claims 1, 2, 12-14, 16-19, 20-25, 32-40, 43-46, 54 and 55 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. taken with both Jones et al. and Chen et al. ('813), in further view of Tice et al. (U.S. Patent 4,389,330).

The teachings of Chen et al., Jones et al. and Chen et al. ('813) are applied as above for claims 1, 2, 12-14, 16-19, 23, 25, 32-40, 43-46, 54 and 55. Chen et al., Jones et al. and Chen et al. ('813) do not specifically teach removing the organic solvent from the aqueous phase by evaporation, heating, extraction or by applying vacuum (claims 20-22 and 24). However, doing such was routine in the art (see Tice et al., column 4, lines 9-15). It would have been obvious to one of skill in the art to use evaporation, heating, extraction or vacuum to achieve the predictable result of removing the organic solvent from the aqueous solution which comprises the microparticles. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

The applicant argues that both Chen and Jones describe methods for preparing DNA encapsulated microparticles by the double emulsion preparation techniques that include the harvesting of microparticles by centrifugation. The centrifugation steps used by Chen and Jones render their processes non-continuous, as centrifugation necessarily implies the treatment of a discrete batch of product and is therefore not amenable to a continuous process. As a result, Chen and Jones do not describe or suggest a "scalable continuous process" for the preparation of microparticles, as is required by claim 1.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). None of Chen and Jones have to teach each and every claim limitation. If they did, this would have been anticipation and not an obviousness-type rejection.

The applicant argues that the '813 patent describes methodologies and apparatuses for concurrent flow mixing (referred to as "CFM") of gene therapy vectors and associated vehicles. In the practice of a continuous CFM process, each reagent is continuously fed into a dispenser connected to the mixer whereby it is unnecessary to halt operation of the process to load new reagents into the system (the '813 patent at column 21, lines 47-57). The applicant argues that the '813 patent places significant emphasis on the advantages of CFM as compared to other mixing technologies. Thus, the applicant argues, the '813 patent convey in unambiguous terms that mixing formats other than CFM do not allow for scalable methodologies having the advantages associated with the CFM technique. In view of this teaching, the person of ordinary skill in the art would not have considered the '813 patent as having provided the rationale to use a technique other than CFM by attempting to modify the double emulsion methods of Chen and Jones so as to render them continuous. Instead, the '813 patent would have conveyed to the skilled person the importance of using the CFM technology (in

either a continuous or non-continuous format) for preparing compositions containing a gene therapy vector and a vehicle.

This is not found persuasive because the instant rejection is based on using CFM and not a technique other than CFM(see above). The applicant did not provide any evidence that one of skill in the art would not have been able to use CFM to obtain Chen's microparticles.

The applicant argues that the '813 patent contains no detailed teaching regarding the preparation of nucleic acid-containing microparticles and provides no instruction as to how the impediment to a continuous process presented by a centrifugation step might be overcome.

This is not found persuasive because a centrifugation step is not required in the CFM method. Again, the rejection is based on modifying Chen by using CFM, i.e., no centrifugation step. Furthermore, the statement that the '813 patent does not teach the preparation of nucleic acid-containing microparticles is incorrect, as the invention of the '813 patent is drawn to the preparation of nucleic acid-containing microparticles (see column 4, lines 12-60).

The applicant argues that the '813 patent contains no instruction as to how to harvest microparticles in the absence of a centrifugation step so as to permit the performance of a continuous double emulsion technique.

This is incorrect. The apparatus taught by the '813 patent comprises collection means and thus, the continuous process does not need a centrifugation step (see Fig. 1, column 19, lines 13-61, column 21, line 52 through column 52, line 4, column 23, line 35-45).

The applicant argues that none of Shah, Parikh, Hartounian, Hedley, and Tice remedies the deficiencies noted above. This is not found persuasive because there is nothing to be remedied in the combined teachings of Chen, Jones and the '813 patent.

Conclusion

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ileana Popa/
Primary Examiner, Art Unit 1633